that it is thrombus which causes the arterial obstruction and symptoms after cortisone has been given, and it might be argued that there is an indication for the use of anticoagulants during and following cortisone therapy.

Summary

Two cases of giant-cell arteritis—one with the formation of saccular aneurysms—in a woman of 56 and a man of 76 are presented. Treatment was respectively with cortisone orally and A.C.T.H. by injection. Both patients recovered. The histological findings both before and after treatment are described and illustrated. A possible explanation of why aneurysms occur only in the larger vessels in giant-cell arteritis is offered. The advantages of a second biopsy after completion of treatment, with a view to assessing the degree of structural recovery, are pointed out.

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GIANT-CELL ARTERITIS OF THE LEGS

BY

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[WITH SPECIAL PLATE]

Giant-cell or temporal arteritis was described clinically by Hutchinson in 1890, but it was not until 1934 that Horton *et al.* recognized the histological features. The condition was initially believed to be localized to the temporal arteries, but of recent years it has become apparent that it may be a generalized arterial disease. Visual disturbances and cerebral symptoms are frequent complications, but the development of gangrene in the limbs has rarely been mentioned, and it is for this reason that the following case is thought to be worth recording.

Case Report

A woman aged 75 was admitted to St. Bartholomew's Hospital on July 14, 1954, complaining of pain in both feet. She had suffered with cold feet and chilblains for many years, but these had caused her no serious inconvenience until three months before admission, when she developed a sudden severe pain in both legs, the left leg being the more painful. The legs became white, and were swollen to a level above her knees. A diagnosis of "thrombosis" was made, and after twelve days' confinement to bed the pain and swelling subsided and the colour returned to normal. When she became ambulant she noticed that her feet were colder than before, and that they were blue and stiff. The feet and legs became increasingly painful, but she persisted with her daily housework until two weeks before admission. Following the "thrombosis" she noted that her general health had deteriorated; she had felt a little feverish towards the evening, her appetite had gradually worsened, and tiredness had become a prominent feature.

She was a pale woman with bilateral cataracts. The fundi showed choroidal pigmentation, the veins were normal, but the arteries were sclerosed. There was no evidence of temporal arteritis. Her heart was clinically not enlarged. Her arms were normal. B.P. 140/70; T. 99° F. (37.2° C.); P. 80; R. 22.

Legs.—Left: The foot was swollen and the skin waxen in appearance. The distal half of the foot was cold and dark blue, with patches of white on the toes. The remainder of the foot and limb was warm and of a normal colour. *Right:* The distal third of the foot was cold and dark blue apart from the toes, which were white; the remainder of the foot and limb was warm and of a normal colour; the femoral and popliteal pulses were present in both legs, but pulsation could not be felt in either foot.

Investigations.—Hb, 10.4 g. per 100 ml.; W.B.C., 16,000 per c.mm.; E.S.R., 25 mm. in one hour (Westergren); serum proteins, 6.7 g. per 100 ml. (albumin 3.9 g., globulin 2.8 g.); blood urea, 34 mg. per 100 ml. Urine: No albumin or sugar detected; a centrifuged deposit showed an occasional white blood cell, a few epithelial cells, and red blood corpuscles (one to two in an occasional 1/6 field). Wassermann and Kahn reactions were negative.

X-ray Examination.—Chest film: slight ventricular hypertrophy; lung fields clear. Intravenous pyelogram: both kidneys functioned promptly, with a good concentration. Leg films: there was evidence of a minor degree of vascular calcification.

Operation.—A below-knee amputation of the left leg was performed with a right lumbar sympathectomy on July 16.

Pathological Examination of Left Leg

Except for peripheral gangrene, the only pathological changes noted on dissection of the limb were in the larger arteries, which resembled firm cords. Atheromatous plaques were not evident on macroscopical examination, but the vessel walls showed multiple minute foci of calcification. The accompanying venae comitantes were small, but the vessels were fully patent except for a little recent blood clot in a small lateral plantar vein. The long and short saphenous veins were normal.

Microscopical examination of the anterior tibial, posterior tibial, and peroneal arteries showed essentially similar histological changes. The lumen was either completely obliterated or reduced to a narrow chink by thickening of the intima, resulting from a proliferation of loose, fairly vascular mesenchymal tissue infiltrated with small numbers of chronic inflammatory cells, predominantly lymphocytic in type (Special Plate, Fig. 1). Small foci of atheromatous fatty change were also present in some sections. The internal elastic lamina of the vessels was reduplicated and stained irregularly; the inner fibres, in general, stained indifferently, while the outer fibres appeared highly refractile, and in many areas were closely related to fine or heavy deposits of calcium. The elastica showed some fragmentation, but complete loss of a segment of the internal elastic lamina was seen in two sections only, and at both sites the deficiency was anatomically related to a calcified plaque in the adjacent inner media (Plate, Fig. 2).

There was an intense diffuse cellular infiltration of the media composed mainly of lymphocytes, but also including moderate numbers of histiocytes together with varying numbers of multinucleated giant cells, many with peripherally arranged nuclei, and showing, in some fields, a focal arrangement simulating tuberculous follicles (Plate, Fig. 3). Small to moderate numbers of plasma cells were also identified (Plate, Fig. 4), but neutrophil and eosinophil leucocytes either were absent or were present in very small numbers. The media showed increased vascularity, fibro-

blastic proliferation, multiple foci of calcification, together with vacuolation and some eosinophilic granular debris which was probably derived from degenerate and necrotic smooth muscle cells. In general, normal muscle cells were present only as a thin, irregular peripheral zone adjacent to the adventitia (Plate, Fig. 3). The latter showed fragmentation and destruction of the external elastic lamina with increased fibrosis and slight or minimal lymphocytic cellular infiltration. Ziehl–Neelsen stained sections were negative for acid-fast bacilli. The accompanying venae comitantes showed only slight subintimal thickening and medial fibrosis with no evidence of thrombosis or phlebitis.

The dorsalis pedis artery showed changes similar to those seen in the large arteries except that the narrowed lumen was occluded by a small recent thrombus and that the media of the vessel appeared normal except for some calcification and slight cellular infiltration with lymphocytes and histiocytes. The medial and lateral plantar arteries showed only slight intimal thickening with proliferation of the elastica and slight medial fibrosis. A small lateral plantar vein contained recent thrombus; the other veins showed no significant histological changes. Sections of the smaller vessels of the foot (arcuate, dorsal metatarsals, plantar metatarsals, and digitals), together with adjacent soft tissues, showed widespread acute inflammatory changes. Microscopical examination of the tibialis anterior muscle showed no abnormality. A section of the soleus muscle included a small artery which showed intimal thickening with fairly extensive chronic inflammatory cellular infiltration of the media and adventitia, including small numbers of multinucleated giant cells.

The lesions in the larger arteries of the amputated limb were considered to be those of giant-cell (temporal) arteritis, and a diagnosis of giant-cell arteritis complicated by gangrene of the foot was made. The medial calcification and relatively slight atheromatous changes were regarded as incidental, additional findings. The acute inflammatory changes in the smaller pedal vessels appeared to be non-specific in nature and almost certainly secondary to the gangrenous process.

After the operation the right leg became painless and warmer, and the colour improved. A course of Buerger's exercises was started on the right leg, but on the fourth post-operative day obvious gangrene of the big toe, with oedema and discoloration of the foot, had occurred.

Cortisone was started, but only 150 mg. had been given when it was apparent that surgery must be undertaken to prevent spread of the gangrene.

Operation.—A below-knee amputation of the right leg was performed on July 30.

After each of the amputations a transfusion of 1 pint (570 ml.) of whole blood was given. Recovery from these operations was satisfactory and uneventful. Both stumps healed by first intention and were free of pain. On discharge from hospital she was extremely well; her appetite had returned to normal and she was apyrexial. She was seen again in November on her way to Queen Mary's Hospital, Roehampton, where she was to be fitted with bilateral prostheses. Her general health had remained good and the stumps showed no sign of ischaemia. The E.S.R. had fallen to 9 mm. in one hour (Westergren).

Pathological Examination of Right Leg

Dissection of the anterior tibial, posterior tibial, and peroneal vessels showed changes similar to those observed in the previously amputated left leg. The small arteries of the foot also appeared abnormally thick-walled and stenosed. The firm, cord-like arteries showed little macroscopical evidence of atherosclerosis or of extensive calcification. The distal segment of the anterior tibial artery contained a small central plug of red thrombus. The accompanying venae comitantes were small, but fully patent.

Microscopical examination of the anterior tibial, posterior tibial, and peroneal arteries showed pathological changes similar to those seen in the corresponding vessels of the left leg. The accompanying venae comitantes were essentially normal except that one section of an anterior tibial vein showed a small, cellular intramural focus composed of lymphocytes and small numbers of histiocytes.

Microscopical examination confirmed that the arteritis also involved the dorsalis pedis, medial plantar, and arcuate arteries, all of which showed gross intimal thickening with extensive lympho-histiocytic cellular infiltration and associated muscle-cell degeneration of the media. Sections of the medial plantar artery also showed moderate calcification and giant-cell infiltration of the media. The lateral plantar artery and two dorsal metatarsal arteries showed minimal specific inflammatory changes, and the one plantar metatarsal artery sectioned had a normal media with only slight intimal proliferation. Acute inflammatory changes seen in the walls of the digital vessels were similar to those observed in the left foot and were likewise considered to be non-specific and to be related to the peripheral gangrene.

Serial sections of a block taken from the tibialis anterior muscle included three small arteries showing focal lympho-histiocytic cellular infiltration of the media, adventitia, and perivascular connective tissue with, in one vessel, calcification and associated giant-cell reaction (Special Plate, Fig. 5); other small vessels included in the section appeared normal. Section of one of the long flexor muscles showed occasional small focal collections of lymphocytes situated in the interstitial tissue between the muscle fibres, but the few small vessels included in the section were normal.

Discussion

The clinical findings of fever, anorexia, anaemia, and arterial disease in this case are consistent with a diagnosis of giant-cell arteritis, which is further established by the almost pathognomonic histological changes in the affected arteries. Comparison of the vascular lesions in the two limbs showed a close similarity in the histological changes with only a slight difference in anatomical distribution. Both limbs showed extensive involvement of tibial and peroneal arteries, and while the arteritis in the left leg appeared to fade peripherally at the level of the dorsalis pedis it had extended, on the right side, into the plantar and arcuate vessels. Involvement of small muscle arteries was noted in both specimens, and it is possible that muscle biopsy has a place in the diagnosis of giant-cell arteritis if biopsy of a large artery is contraindicated.

The interesting features of this case are, firstly, the atypical clinical presentation of the disease with its complete absence of symptoms referable to arteritis of any of the cranial vessels and its apparent localization to the arteries of the lower limbs, and, secondly, that the vascular changes were complicated by the development of peripheral gangrene.

Harrison (1947–8) has emphasized the ophthalmic and cerebral complications of this condition, but states that it is certainly significant that, in a disease which causes gross vascular narrowing and affects medium-sized arteries, there is no ischaemic gangrene of the limbs. Harrison refers to one of the cases of temporal arteritis described by Robertson (1947) which developed gangrene of a toe, necessitating amputation. The gangrene was thought to be due to obliterative arteriosclerosis and not to giant-cell arteritis, but the blood vessels in the amputation specimen were not examined histologically. Only two of the 75 cases reviewed by Harrison (1947–8) showed histological evidence of femoral arteritis, and in one other case there was clinical evidence of involvement of a dorsalis pedis artery. Cardell and Hanley (1951) reviewed 27 reported cases of giant-cell arteritis in which necropsy had been performed, and, although the series emphasized the diffuse nature of the vascular lesion, none of the cases had developed peripheral gangrene, and extensive involvement of limb vessels was not recorded. It is, however, impossible

to assess the true extent of the vascular lesions from many of these case reports as post-mortem examination was frequently incomplete.

More recently, Heptinstall *et al.* (1954) have reported 14 cases of giant-cell arteritis, three of which came to necropsy. Vascular changes were widespread in the three fatal cases, and included histologically confirmed lesions in the right femoral artery and left popliteal artery in one case, and in the right popliteal artery in a second case. Pains in the limbs and joints were noted in 5 of the 14 cases—the authors suggested the possibility that the limb pains may be due to specific changes in the arteries—but peripheral gangrene was not encountered. Reference, however, is made to a case reported by Frangenheim (1951) in which a 72-year-old man had suddenly become blind and in which amputation of a leg for gangrene revealed the changes of giant-cell arteritis in the femoral artery. Reference is also made to a case described by Atlas (1943) in which a 68-year-old woman had a leg amputated for gangrene. The case was recorded as one of Buerger's disease, but we agree with Heptinstall *et al.* (1954) that the histological findings are consistent with giant-cell arteritis. In this case the patient died shortly after operation, but whether a necropsy was performed is not recorded.

It is thus apparent that giant-cell arteritis can involve the arteries of the lower limbs and in rare instances be complicated by gangrene. Giant-cell arteritis is a disease of the middle-aged and elderly, and it is therefore very probable that affected limb arteries will also show some degree of incidental atherosclerosis; but unless the latter is extensive it is reasonable to suggest that ischaemic symptoms which may develop are due mainly to the obliterative arteritis which is a well-recognized feature of giant-cell arteritis.

Giant-cell arteritis should therefore be considered in the differential diagnosis of any unexplained case of peripheral vascular disease occurring in the middle-aged or elderly, and if such a diagnosis is substantiated corticotrophin or cortisone therapy should be given before gangrene supervenes and surgery becomes imperative.

Summary

A case of giant-cell arteritis apparently localized to the arteries of the lower limbs and producing gangrene is reported. Both legs had to be amputated, and histological examination showed the typical features of giant-cell arteritis in the tibial and peroneal arteries. One limb also showed involvement of the pedal arteries, and essentially similar changes were noted in some of the small arteries supplying voluntary muscles.

A review of the literature indicates that peripheral gangrene is a rare complication of giant-cell arteritis, but the real incidence of involvement of the leg arteries in this disease is not known. The apparent rarity of this condition may account for its being overlooked in other cases, and it is suggested that giant-cell arteritis should be considered in the differential diagnosis of any unexplained case of peripheral vascular disease occurring in the middle-aged or elderly.

We are indebted to Mr. E. G. Tuckwell for permission to publish this case and to Professor J. W. S. Blacklock for his help and advice. We thank Mr. K. W. Iles for the photomicrographs and Miss Audrey Dixon for the cutting and staining of many sections.

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NASAL GRANULOMA AND PERIARTERITIS NODOSA

REPORT OF A CASE

BY

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[WITH SPECIAL PLATE]

Since Kussmaul and Maier (1866) gave the name "periarteritis nodosa" to a disease which they were the first to describe, many cases differing in certain clinical and pathological details have been reported. In 1903 Veszprémi and Jancsó made the diagnosis from histological material in a case presenting no gross evidence of the disease; and Mönckeburg (1905) for the first time described lesions of periarteritis in the lungs. The second case with pulmonary-artery involvement, reported by Ophüls (1923), had many distinguishing features, among them granulomatous lesions in serous membranes. Gradually it came to be appreciated that the microscopic form of the disease, affecting small arteries and veins, was the commoner and could be distinguished from the classical disease (Zeek *et al.*, 1948; Zeek, 1952).

Cases of periarteritis nodosa with granulomatous lesions in the upper respiratory tract are uncommon. Godman and Churg (1954), who reported seven cases of their own, were able to find 22 cases in the world literature. Of these, one reported by Howells and Friedmann (1950) and two reported by Stratton *et al.* (1953) are the only British cases in their list. Klinger (1931) was the first to describe a syndrome of severe destructive sinusitis, nephritis, and uraemia. Wegener (1936, 1939), describing three cases of ulcerative granulomata in the upper respiratory tract with periarteritis nodosa, wrote: "The point of origin of the disease was the inner nose, where a putrid, necrotic inflammation was found with granulation tissue and nodular granulomata. This evidently led to sensitization of the body as a whole, resulting in allergic, hyperergic reactions, especially in the vascular system." Stratton *et al.* (1953) stressed that "the essence of this syndrome is that the upper respiratory tract lesions are the first and, at the onset, the dominating feature of the condition." Pulmonary lesions, both vascular and granulomatous, are almost a constant feature of this syndrome; in only one case of the series reviewed by Godman and Churg were they absent. In this case, reported by Lindsay *et al.* (1944), there was a progressive destructive nasal lesion for a year before acute fatal periarteritis nodosa developed.

The case now reported appears unique in two respects: (1) the acute nasal and gingival giant-cell granulomatous lesions regressed and healed before the fatal illness; and (2) no vascular or granulomatous lesions could be found in the lungs at necropsy.

Case Report

A 41-year-old housewife had an upper right premolar extracted in May, 1954. The socket healed well till about June 17, when a bright-red swelling appeared on the gum, which became painful. Two lower left molars were extracted at this time, the sockets failing to heal and becoming swollen and painful. The face then began to swell and she had headaches and nasal discharge. She felt weak

R. FINLAYSON AND J. O. ROBINSON: GIANT-CELL ARTERITIS OF LEGS

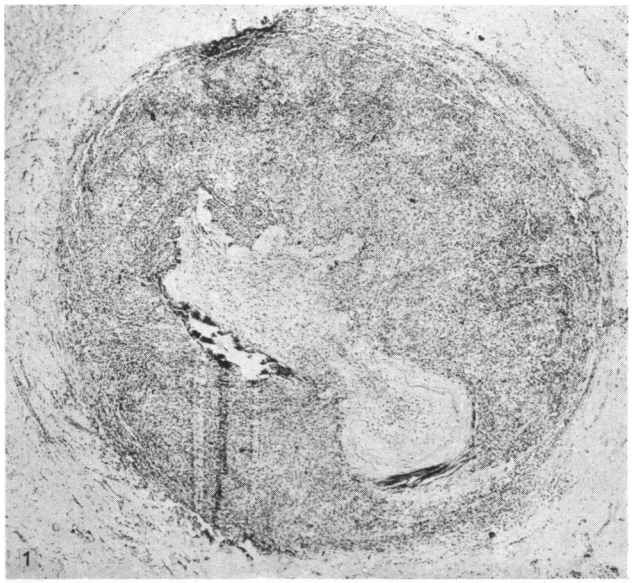


FIG. 1.—Left posterior tibial artery: occlusion of lumen by connective tissue containing moderate numbers of cells, with diffuse cellular infiltration of media. (Haematoxylin and eosin. ×24.5.)

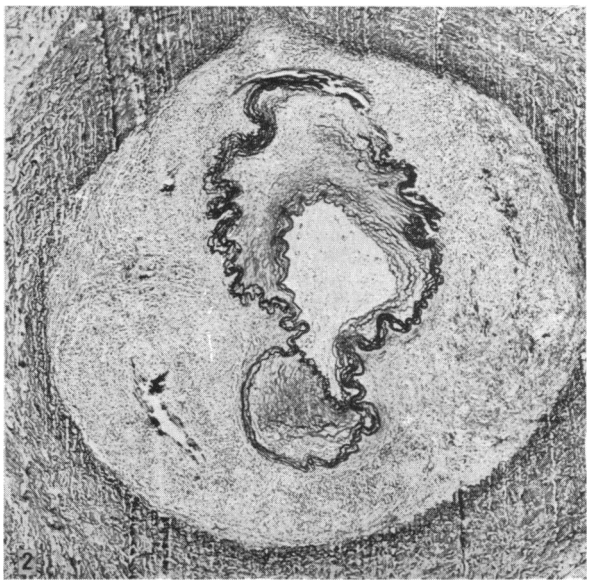
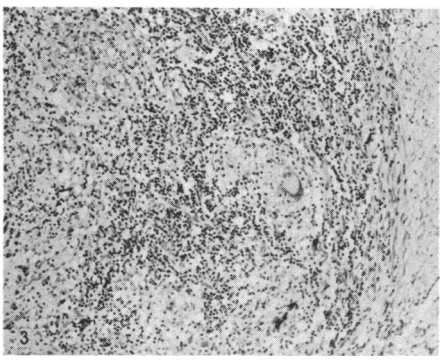


FIG. 2.—Left anterior tibial artery: proliferation, splitting, and bulging of internal elastic lamina. Small segmental deficiency of lamina adjacent to calcified medial plaque. (Weigert-van Gieson. ×28.)



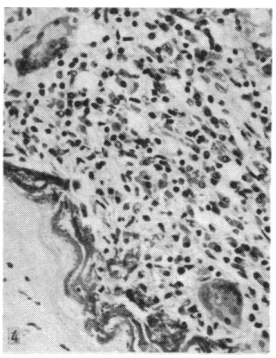


FIG. 3.—Part of wall of left anterior tibial artery: intense chronic inflammatory cellular infiltration of media, with foci simulating tuberculous follicles. Smooth-muscle cells clearly identified only by adventitia on right. (H. & E. ×75.)

FIG. 4.—Left posterior tibial artery: infiltration of media with giant cells, lymphocytes, plasma cells, and histiocytes. Irregular staining of internal elastic lamina with calcification. (Haematoxylin and eosin. ×165.)

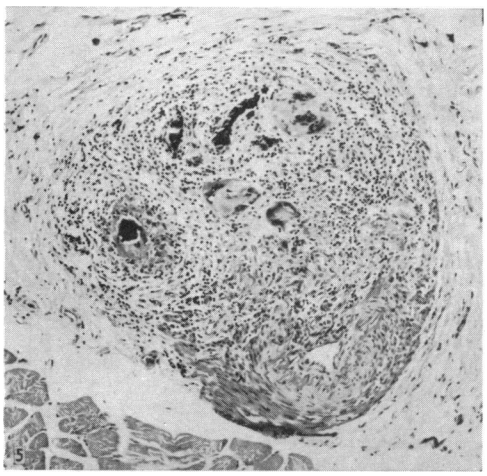


FIG. 5.—Small artery from right tibialis anterior muscle: focal infiltration of media, adventitia, and perivascular connective tissue with lymphocytes and giant cells, the latter related in part to small areas of calcification. (Haematoxylin and eosin. ×80.)

P. F. MILNER: NASAL GRANULOMA AND PERIARTERITIS NODOSA

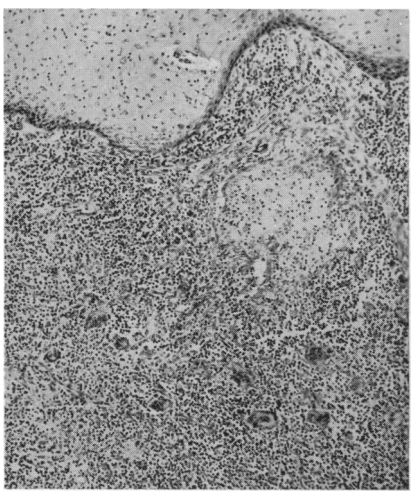


FIG. 1.—Biopsy of gingival tumour, showing multinucleate giant cells in the dermis. (Haematoxylin and eosin. ×60.)

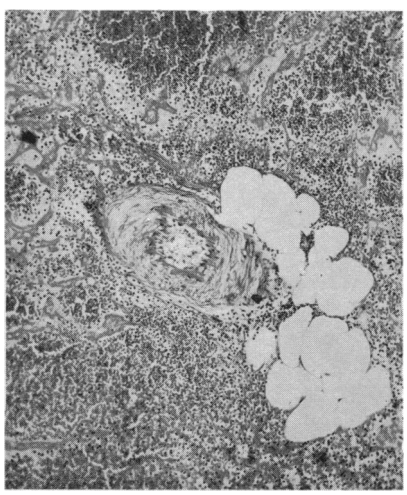


FIG. 2.—Skin over right deltoid: normal vessel in subcutaneous fat surrounded by organizing haemorrhage. (H. & E. ×65.)

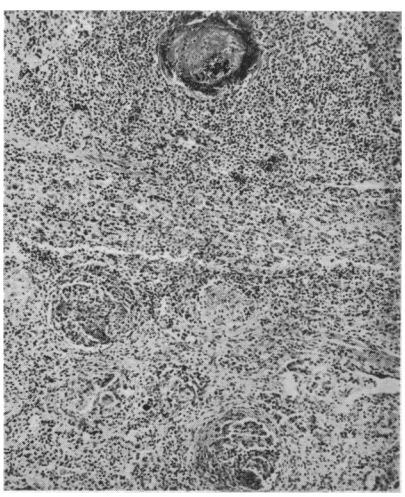


FIG. 3.—Kidney, showing hyaline necrosis and fibrosis of glomeruli with oedema and inflammatory exudate. (H. & E. ×60.)